REMARKS

Claims 1-7 and 9-22 are currently in the application.

In the Office Acton mailed February 20, 2004, claims 1-7 and 9-22 continue to be rejected under 35 U.S.C. § 103(a) as being unpatentable over a collection of three references, the Physician's Desk Reference (PDR), Story et al., U.S. Patent No. 4,944,949, and Martin-Algarra et al., International Journal of Pharmaceutics 122, (1,2), 1-8 (1995).

It is the Examiner's position that the PDR teaches an oral formulation of amiodarone tablets and that amiodarone is slightly soluble in water; that Story et al. teach a pharmaceutical delivery system of non-ionic hydrophilic surfactants for poorly water soluble active agents such as NSAIDs, and that Martin-Algarra et al. teach compositions of amiodarone in a non-ionic hyrophilic surfactant such as polysorbate 80. The Examiner maintains that it would have been obvious to have administered amiodarone orally in a non-ionic hydrophilic surfactant composition since the PDR teaches that amiodarone is slightly soluble in water and the surfactant systems of Story et al. demonstrate the solubilization of insoluble drugs such as NSAIDs, and because both the NSAIDs of Story et al. and the antiarrhythmics of the instant application are known to be poorly water soluble. Motivation to formulate amiodarone and dronedarone in a hydrophilic anionic (sic. non-ionic) surfactant would come from the need for a rapidly absorbed orally available antiarrhythmic such as amiodarone. Additionally, absorption would be expected to be improved as taught by Martin-Algarra et al., thereby providing additional motivation.

The rejection is again respectfully traversed and reconsideration thereof is requested. As previously pointed out by Applicants, the PDR not only discloses that amiodarone is slightly soluble in water, as noted by the Examiner, but it also teaches that amiodarone is slowly and variably absorbed; that mean plasma concentrations include considerable individual variability, and that food significantly affects amiodarone absorption [e.g. it increases the area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) by a factor of 2.3 and 3.8, respectively and decreases the time to peak plasma concentration (T_{max}) by 37%]. This, of course, is the very problem addressed by applicants' invention. The absorption profile of amiodarone was known at least as early as 1985 when it was first approved for use, and yet, despite the 1990 Story et al. patent and the 1995 Martin-Algarra publication, the disclosures of which the Examiner urges would have made the solution provided by the instant invention obvious, the 2001 PDR entry for

amiodarone indicates that the absorption problem has not yet been solved. In other words, although the slow and variable absorption by amiodarone has been known for more than 15 years and the teachings of Story et al. have been available for more than 10 years, increasing the absorption of amiodarone and reducing its variability have until now remained long-felt but unmet needs even with the additional motivation purportedly provided more than 5 years ago by Martin-Algarra et al. Had the cited prior art made the instant invention obvious, as urged by the Examiner, it would seem that the absorption problem related to amiodarone would have been solved long ago. Hence, it is respectfully submitted that the cited references not only fail to suggest applicants' invention, but outline a long-felt need for the instant compositions.

Although the Martin-Algarra reference discloses the use of an *in situ* rat gut technique in which a solution of polysorbate 80 containing amiodarone hydrochloride was perfused directly into the small intestine of the rat to study intestinal absorption of amiodarone, the reference, as noted by the Examiner, does not teach oral administration or the use of dronedarone. Moreover, nowhere in the reference is there a disclosure of Applicants' formulation in which a nonionic hydrophilic surfactant is present in a proportion of from 1% to 50% by weight of the active principle. In fact, the reference specifies that the lowest concentration of surfactant tested [i.e., 0.4 mM (5 mg) or 704% relative to the active ingredient] is the concentration that "provides the minimal amount of surfactant leading to amiodarone solubilization" (page 5, column 1) and, therefore, actually teaches away from Applicants' invention which requires at least 700 times less surfactant to achieve solubilization and reduce absorption variability. Accordingly, it is submitted that the Martin-Algarra reference not only fails to either teach or suggest Applicants' claimed invention, it actually teaches away from it and is therefore incompetent to support the rejections based thereon.

Moreover, the Story et al. disclosure is directed to the formulation of NSAIDs with surfactants to give micelle-forming compositions primarily intended to protect both the stomach and intestine. Such formulations are stated to contain drug and surfactant in a weight ratio (drug:surfactant) of from 1:5.7 to 1:50. Thus, the surfactant is present in a proportion of from 570% to 5000% relative to the drug whereas the instant claims specify that the surfactant is present in a proportion of from 1% to 50% by weight relative to the active principle. Clearly, there is nothing in Story et al. that would have suggested using such a

small amount of non-ionic hydrophilic surfactant to both increase rate and reduce variability of absorption of either NSAIDs or amiodarone and dronedarone.

In view of the foregoing, it is clear that Martin-Algarra et al. do not suggest Applicants' claimed composition. Nowhere does the reference suggest that the absorption of a benzofuran antiarrhythmic agent in any composition would be enhanced by a nonionic hydrophilic surfactant present in a proportion of 1% to 50% by weight of the active agent. In fact, the reference teaches that the minimum amount of surfactant required is at least 700-fold greater than the amount present in Applicants' composition. Story et al. likewise teaches formulations containing surfactants in a proportion of at least 570% by weight relative to the active ingredient, i.e., at least 570-fold greater than the amount of surfactant in Applicants' compositions, and Story et al. therefore adds nothing to Martin-Algarra et al. Thus, the Martin-Algarra et al. and Story et al. references, considered either individually or in combination with each other and/or the PDR, simply would not have suggested Applicants' compositions, and are therefore manifestly incompetent to support a rejection under 35 U.S.C. § 103(a).

As to the rejection for obviousness-type double patenting over U.S. Patent No. 6,143,778, the Examiner urges that the conflicting claims are not patentably distinct because both are drawn to a pharmaceutical composition of amiodarone and a non-ionic hydrophilic surfactant, and that although the amiodarone of the –778 patent is for parenteral administration, it would have been obvious to lyophilize the compositions of the patent and administer them orally. The rejection is again traversed and reconsideration thereof is requested.

The claims of the –778 patent are drawn to parenteral solutions containing amiodarone hydrochloride, a buffer solution capable of maintaining a pH of 2.4-3.8 and a non-ionic hydrophilic surfactant. The role of the surfactant is to permit preparation of clear, stable, concentrated solutions of active principle which can be subsequently diluted for administration by perfusion. There is nothing in the reference to suggest lyophilizing the mixture of active agent, buffer and surfactant to prepare a solid oral preparation nor is there anything to suggest that oral administration of such a mixture would enhance the rate of absorption and reduce its variability. Thus there is nothing in the –778 patent that would render the instant claims obvious and hence the patent is not a proper basis for a double patenting rejection and the withdrawal thereof is respectfully requested.

Claims 1-7 and 9-22 are directed to solid pharmaceutical compositions for oral administration containing an antiarrhthmic benzofuran derivative and a nonionic hydrophilic surfactant in a proportion of from 1% to 50% by weight of the benzofuran derivative, which compositions solve the long-felt but unmet needs of increasing absorption and reducing variability. There is nothing in any of the cited references considered individually or in any combination that would fairly teach or suggest such compositions, and accordingly, the rejections based thereon should be withdrawn.

There being no remaining issues, this application is believed in condition for favorable reconsideration an early allowance and such actions are earnestly solicited.

Respectfully submitted,

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